Trimetazidine as Adjunctive Therapy for Decreasing Major Adverse Cardiac Events in Coronary Artery Disease Patients Undergoing Reperfusion Strategy: A Meta-analysis of Randomized Controlled Trials

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Abstract

Trimetazidine as adjunctive therapy in cardioischemic patients has shown improvement in angina and left ventricular ejection fraction, but with conflicting evidence on hard clinical outcomes. This meta-analysis aims to compare the efficacy of trimetazidine versus placebo in reducing cardiac mortality and major adverse cardiac events (MACEs) in coronary artery disease patients after reperfusion strategies, whether percutaneous coronary intervention or thrombolysis. The primary outcomes examined were cardiac mortality and combined MACEs; secondary outcomes were repeat revascularization, heart failure after reperfusion, stent restenosis, recurrence of angina, and reinfarction. Trimetazidine in comparison to placebo was associated with lower cardiac mortality and combined MACEs, but results were not significant. Among secondary outcomes, only stent restenosis was significantly reduced (risk ratio, 0.53; 95% confidence interval, 0.34–0.83; $P = 0.006$). Further trials should be conducted with more standard dosing regimens, duration of therapy, and similar severities of ischemic disease.

INTRODUCTION

In coronary artery disease, during myocardial ischemia and infarction, underlying metabolic and functional abnormalities often aggravate cardiac injury. Recent pharmaceutical agents have been developed to avoid this by modifying cardiomyocyte function. In particular, trimetazidine, an antianginal agent that selectively inhibits long chain-3-ketoacyl CoA thiolase activity, has been found to reduce fatty acid oxidation and stimulate glucose oxidation. This helps improve myocardial energy phosphate levels, subsequently increasing myocardial ischemic tolerance without causing a negative inotropic effect.[1] Trimetazidine also has no vasodilatory properties at rest or during exercise and does not affect coronary flow or blood pressure, allowing it to be combined with conventional pharmacotherapy for coronary artery disease.[2]

Several studies support the benefit of trimetazidine as adjunctive treatment in cardioischemic patients, citing decreased hospitalization and improved cardiac function in chronic heart failure. Stable anginal patients have had lowered attacks and nitroglycerin usage, with improved exercise duration in the TRIMPOL I study. Also, patients with chronic stable angina given trimetazidine for 6 months had significantly greater left ventricular function and improved diastolic function as seen in smaller left ventricular diastolic and systolic diameters and volume indices on echocardiography. Use of trimetazidine in patients who underwent percutaneous coronary intervention (PCI) improved left ventricular ejection fraction and decreased angina incidence.[2] However, conflicting results have been reported on its effect on major adverse cardiac events (MACEs) and cardiac mortality.

Previous meta-analysis on trimetazidine has been conducted among patients with stable angina pectoris, as well as those with ischemic or dilated cardiomyopathy. A meta-analysis reviewed 11 randomized clinical trials and found that stable angina pectoris patients who were given trimetazidine had significantly improved left ventricular ejection fraction and significantly reduced left ventricular end-systolic volume as compared with the placebo group.[2] Other meta-analysis showed significant differences in left ventricular ejection fraction and left ventricular end-systolic volume among cardiomyopathic patients given trimetazidine.[2] In a previous meta-analysis by Li et al,[3] which included six clinical trials and one retrospective cohort, trimetazidine was compared with placebo. The study concluded that adjunctive trimetazidine therapy had a beneficial effect on total MACEs in acute myocardial infarction patients (odds ratio, 0.33; 95% confidence interval [CI], 0.15–0.74; $P = 0.007$), but there was no difference in all-cause mortality, recurrent nonfatal myocardial infarction, or in hospital adverse events.[3] Their study population included both patients who underwent thrombolysis and PCI. Such evidence has led to the practice of using trimetazidine as adjunctive therapy.

The majority of the earlier trials on trimetazidine demonstrated improvements in mechanistic endpoints such as a longer time to 1-mm ST-segment depression and improvements in echocardiography parameters. Clinically, there has been significant reduction of weekly anginal attacks, use of rescue nitroglycerin, higher total work, and longer exercise duration. This has led to the class IIa recommendation by the European Society of Cardiology in 2019 of the use of trimetazidine as a second-line drug in patients with chronic coronary syndromes whose symptoms are not adequately controlled by existing medicines for angina pectoris or as a preferred antianginal drug in those with low blood pressure.[4]

In contrast to the meta-analysis by Li et al,[3] the recent large ATPCI study demonstrated that there was no significant difference in the pooled cardiovascular outcomes among the trimetazidine and placebo groups for patients undergoing percutaneous intervention. More data are apparently needed to demonstrate the efficacy and safety of trimetazidine in reducing hard cardiovascular endpoints. No antianginal drug has yet been shown to have prognostic benefit in patients who have undergone reperfusion strategies. This meta-analysis aims to investigate the potential of trimetazidine adjunctive therapy in the reduction of MACEs in patients with coronary artery disease, whether they underwent PCI or thrombolysis in addition to optimal medical treatment.

The objective of this meta-analysis was to compare the efficacy of trimetazidine versus placebo for the reduction of cardiac mortality and MACEs in patients with coronary artery disease who underwent reperfusion strategies, defined as either PCI or thrombolysis, as studied in randomized clinical trials.

MATERIALS AND METHODS

Search Strategy

A comprehensive search was performed to retrieve the related clinical studies in MEDLINE/PubMed, Cochrane Library, and Google Scholar with the following search terms: "coronary artery disease" OR "acute myocardial infarction" OR "stable angina pectoris" AND "percutaneous coronary intervention" OR "thrombolysis" OR "reperfusion" AND "trimetazidine" OR "trimetazidine dihydrochloride" AND "randomized controlled trial." Articles were limited to studies involving humans and randomized controlled trials published in the last 20 years in the English language.

Authors were not able to do search on EMBASE, contact organizations, and individuals working in the field and pharmaceuticals that manufacture trimetazidine to help identify additional published and unpublished trials primarily because of restricted resources.

Study Selection

The studies evaluated for this meta-analysis were randomized controlled trials in which participants were patients with coronary artery disease who underwent any reperfusion strategy, regardless of nationality, age, or sex. Intervention given must have been trimetazidine of any administration route, dosage, or duration as compared with placebo. Primary outcome measures analyzed were combined MACEs and cardiac mortality, whereas secondary outcomes evaluated were repeat revascularization, heart failure after reperfusion, stent restenosis, recurrence of angina, and reinfarction. Studies that did not meet the previously stated criteria were excluded, as well as duplicate publications.

Data Collection and Analysis

Data Extraction and Management

Data in the trials were independently extracted and summarized by the authors. Data gathered were used to calculate summary statistics, when necessary, prior to data entry.

Assessment of Risk Bias in Included Studies

Quality assessment was done using the evaluation instrument recommended by Cochrane Collaboration for bias risk assessment.

Measures of Treatment Effect
All patients included in the studies were analyzed in the group to which they were originally randomized (intention-to-treat analysis). Dichotomous outcomes were used to describe both primary and secondary outcomes between the groups. Using the statistical package Review Manager Analyses 5.1.7, precision of the results was adjusted using the fixed-effects model. Results were expressed as risk ratios (RRs) at 95% CI.

Assessment of Heterogeneity and Reporting Biases
Heterogeneity in the studies was assessed using χ^2 and I^2 through Review Manager Analyses 5.1.7. Outcomes were examined through fixed-effects model. Random-effects model was also utilized to properly address the heterogeneity among the results of the trials to strengthen the inference of results. Where we found substantial heterogeneity between studies ($P < 0.05$ or $I^2 > 50\%$), we explored possible reasons for this such as duration of treatment.

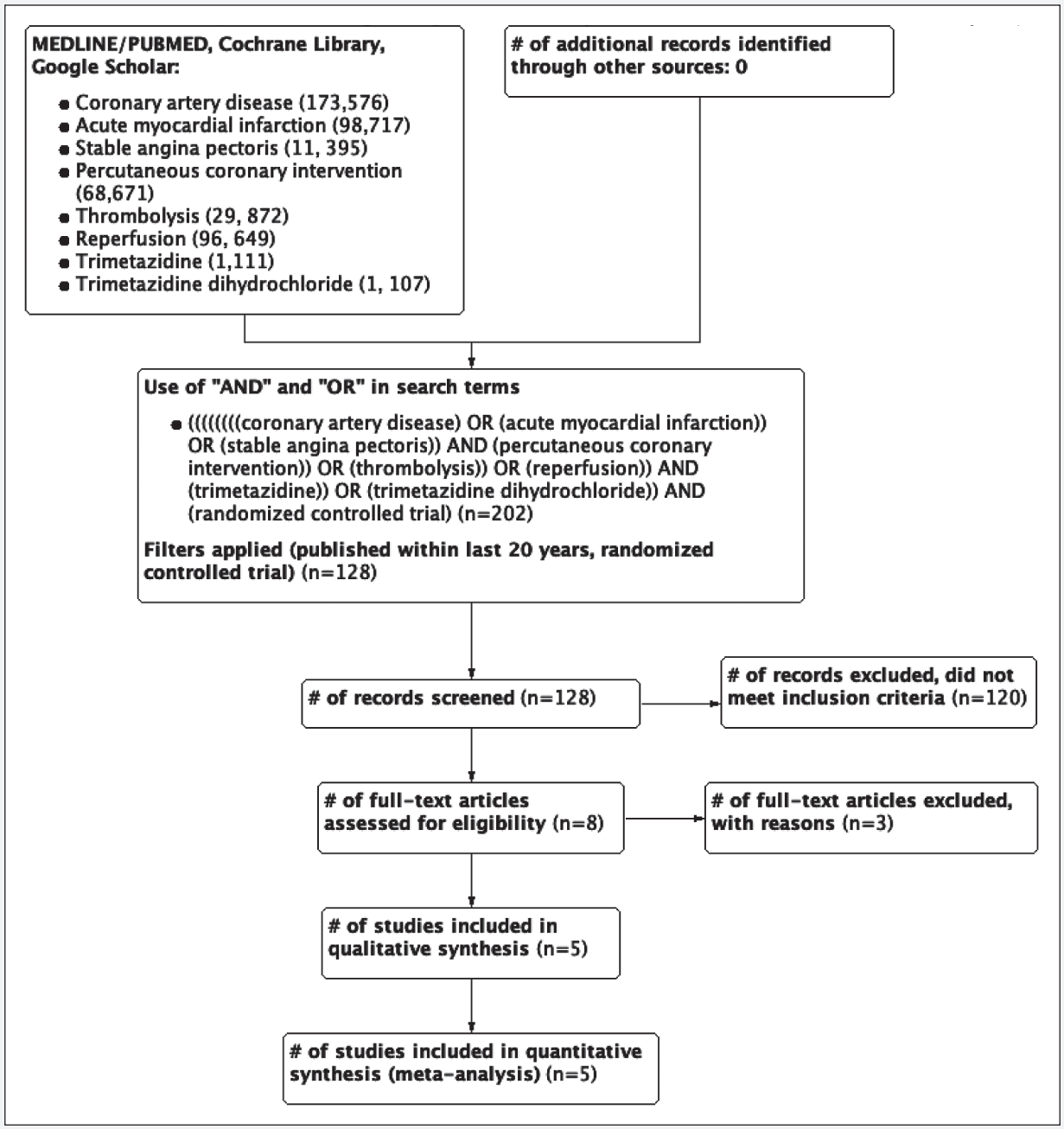

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) study flow diagram showing search results and selection process of literature

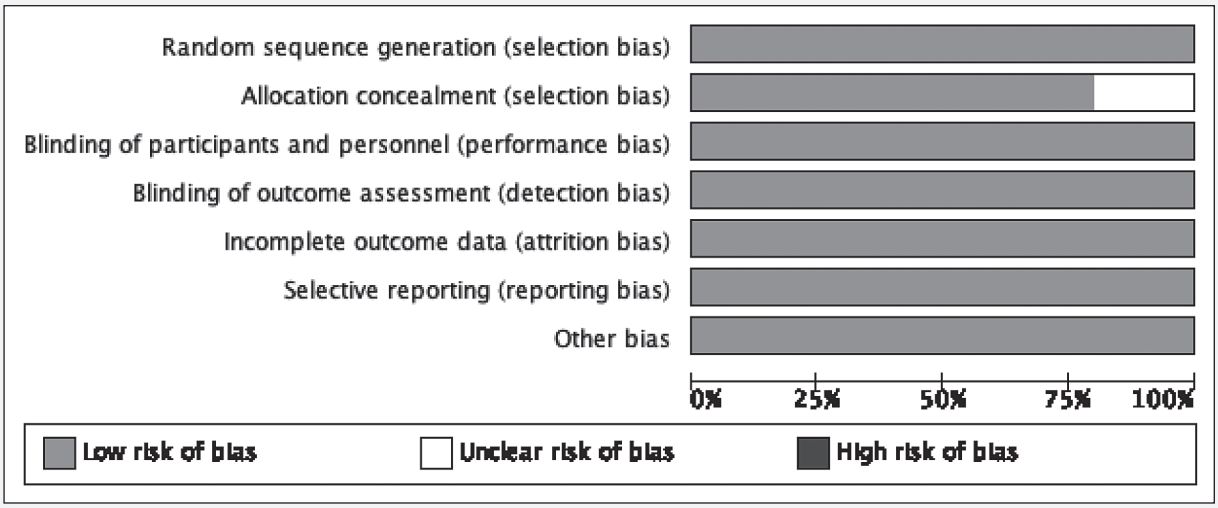

FIGURE 2. Risk-of-bias graph. All studies were generally low risk for bias.

RESULTS

Description of Studies

A total of 202 articles were retrieved by using the search terms in the MEDLINE/PubMed, Cochrane Library, and Google Scholar databases. Limits including clinical trial, randomized clinical trial, and a filter for a 20-year publication time frame were imposed, and the search was narrowed down to 128 articles. From the 128 articles, 120 were excluded as these did not use the target study population, did not have the outcomes specified, or were duplicates. Three of the full text articles were excluded because they were in Chinese language. A total of five valid full articles were used for both the qualitative and quantitative analyses in this study.

Included Trials

All studies identified were randomized controlled trials and evaluated the effect of trimetazidine as adjunctive therapy in patients with coronary artery disease. The studies included patients 18 years or older, with documented coronary artery disease, who went through either PCI or thrombolysis. The dose of trimetazidine varied from 20 to 70 mg and was given via either the oral or intravenous route. The mean duration of intervention ranged from 6 to 47.5 months.

Methodological Quality

Random sequence generation was adequate for all the studies. Allocation sequence was adequate in four studies by Ferrari et al,[5] Shehata,[9] Xu et al,[6] EMIP-FR Group,[8] whereas the remaining study by Chen et al[7] was unclear. Follow-up was adequate in all five studies. Intention-to-treat analysis was also done in all the included studies.

Cardiac Mortality

Cardiac mortality (Figure 4) was reduced in the trimetazidine group as compared with those given placebo among acute coronary syndrome patients who underwent reperfusion, but this was not statistically significant (RR, 0.96; 95% CI, 0.88–

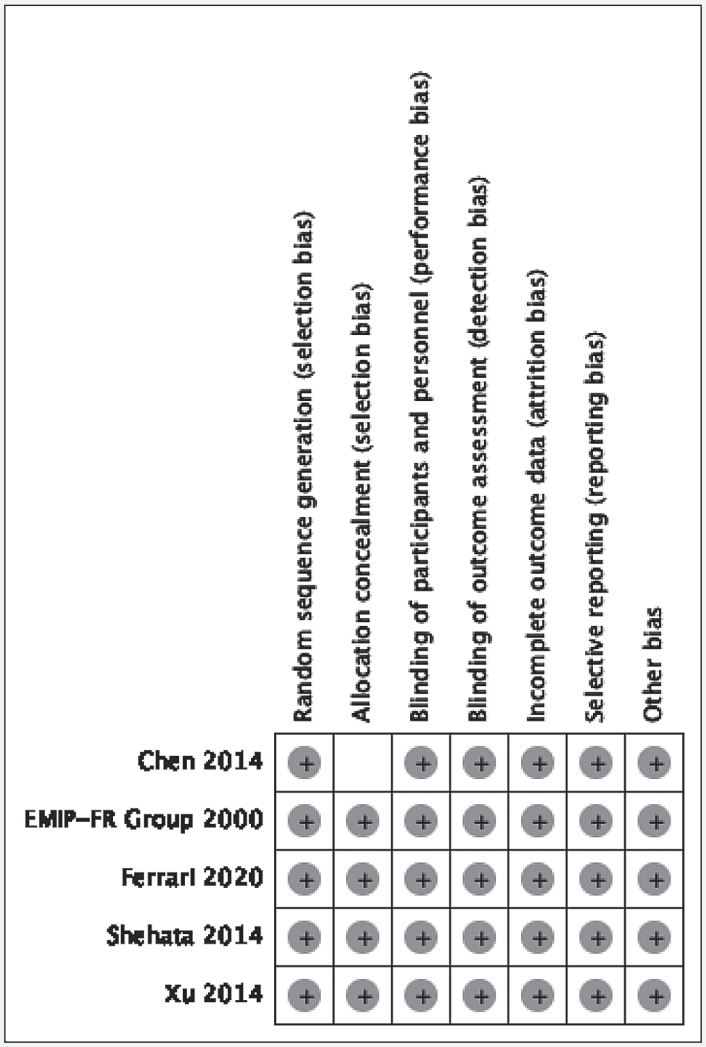

FIGURE 3. Risk-of-bias summary. All studies were generally low risk bias.

TABLE 1. Characteristics of the Included Studies

Study	Country/ Region	Participants (Trimetazidine/ Placebo), n	Age (Trimetazidine/ Placebo), Mean ± SD, y	Male (Trimetazidine/ Placebo), %	Intervention	Reperfusion Strategy	Outcomes	Follow-up Period, mo
Ferrari et al,[5] 2020	Europe, South America, Asia, North Africa	2998/3009	61.1 ± 9.6/ 60.7 ± 9.8	77.1/76.9	Modified-release oral 35 mg twice daily/ once daily in moderate renal failure	Elective or urgent PCI	Death, total MACEs (primary)	47.5
Xu et al,[6] 2014	China	255/255	68.94 ± 3.54/ 68.52 ± 3.06	67.5/68.2	Oral 20 mg three times daily	PCI	Death, total MACEs (secondary)	24
Chen et al,[7] 2014	China	312/323	61.6 ± 11.9/ 60.9 ± 11.6	81.1/76.5	Oral loading dose of 60 mg TMZ the same day after PCI, followed by 20 mg TMZ three times a day for at least 1 mo at discharge	PCI	Death, total MACEs (primary)	11–13
EMIP-FR Group,[8] 2000	France	9871/9854	Not reported	70.3/69.8	40 mg IV loading then continuous IV infusion (60 mg/24 h) for 48 h	Thrombolysis	Death (primary), total MACEs (secondary)	12
Shehata,[9] 2014	Canada	50/50	59.6 ± 5.4/ 58.5 ± 2.3	50/50	70 mg oral loading then 35 mg twice daily	Thrombolysis	Death, total MACEs (primary)	6

IV=intravenous; MACEs=major adverse cardiac events; PCI=percutaneous coronary intervention; TMZ=trimetazidine.

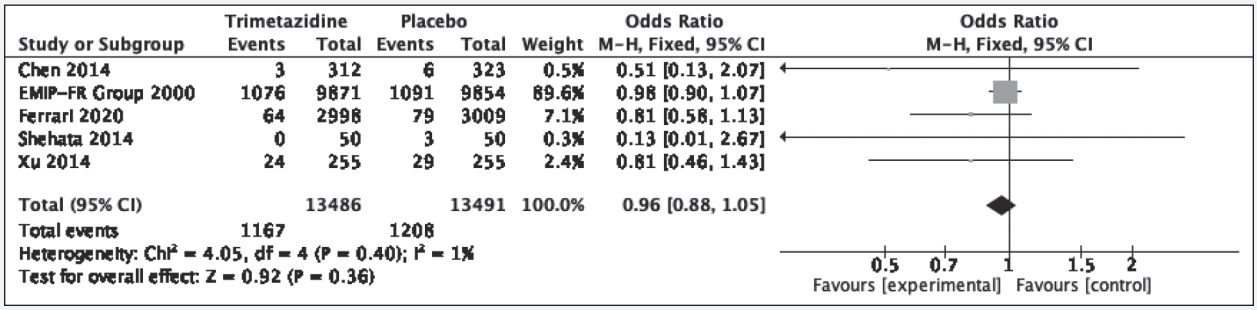

FIGURE 4. The effect of trimetazidine versus placebo on cardiac mortality (fixed-effects model)

1.05; $P = 0.36$). There was no significant heterogeneity among studies ($\chi^2 = 4.05$, $df = 4$; $P = 0.40$; $I^2 = 1\%$).

Combined Major Adverse Cardiac Events

Reporting the incidence of major adverse cardiac events of all the five studies in a pooled fixed-effects model showed significant heterogeneity among populations ($\chi^2 = 13.44$, $df = 4$; $P = 0.009$; $I^2 = 70\%$); hence, a random-effects model was generated.

The random-effects model still showed significant heterogeneity among the five studies ($\chi^2 = 13.44$, $df = 4$; $P = 0.009$; $I^2 = 70\%$), despite the visual inspection of the funnel plots for both forest plots revealing no significant publication bias.

A subgroup analysis was then done to include only studies that gave trimetazidine for at least 1 year, which excluded Shehata.[9] Here, the studies were homogeneous ($\chi^2 = 4.31$, $df = 3$; $P = 0.23$; $I^2 = 30\%$). However, the overall reduction in combined MACEs was not statistically significant (RR, 0.95; 95% CI, 0.89–1.01; $P = 0.08$).

Repeat Revascularization

Trimetazidine was no different as compared with placebo in

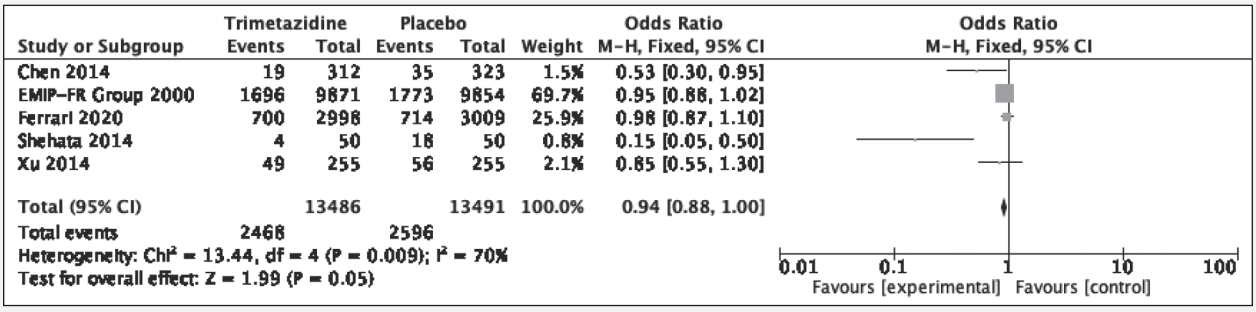

FIGURE 5. The effect of trimetazidine versus placebo on the incidence of major adverse cardiac events (fixed-effects model)

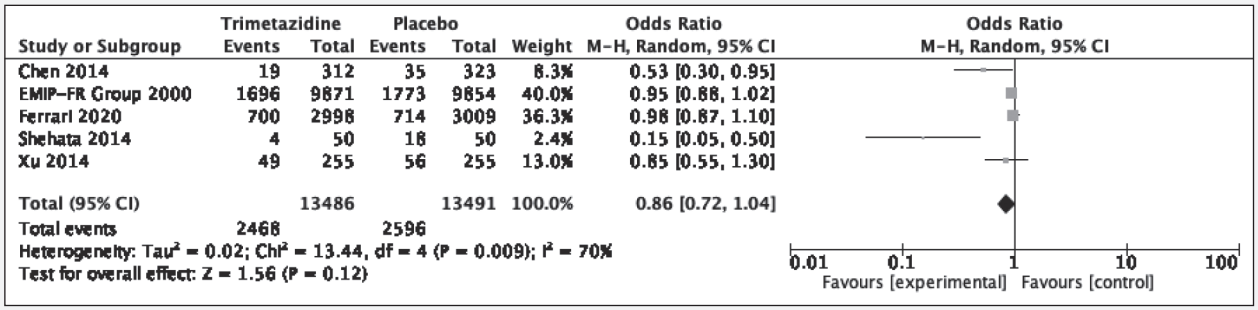

FIGURE 6. The effect of trimetazidine versus placebo on the incidence of major adverse cardiac events (random-effects model)

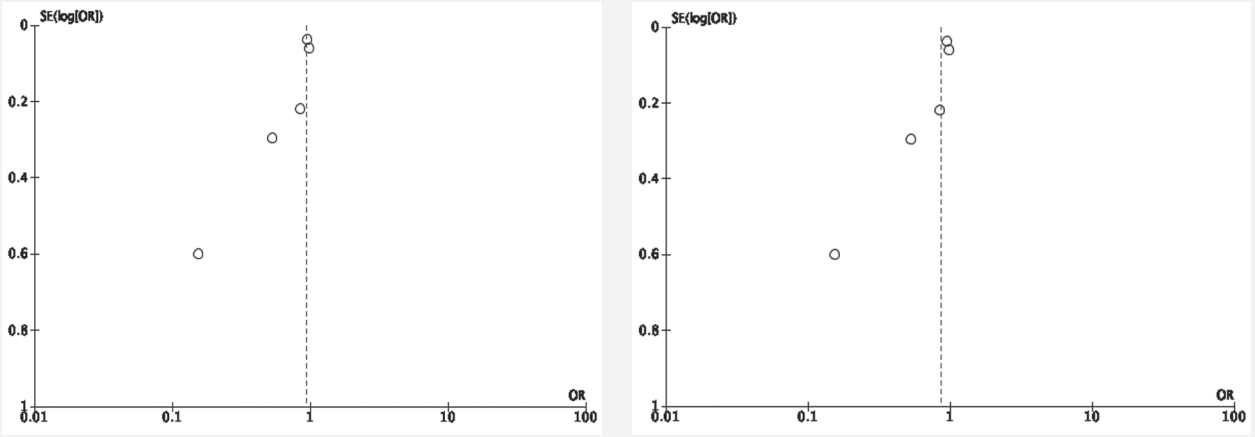

FIGURE 7. Funnel plots of studies included for pooled analysis of combined major adverse cardiac events, for both fixed-effects model (left) and random-effects model (right)

reducing repeat target vessel revascularization (RR, 0.95; 95% CI, 0.83–1.10; $P = 0.52$). No significant heterogeneity was noted among the studies ($\chi^2 = 2.33$, $df = 2$; $P = 0.31$; $I^2 = 14\%$).

Heart Failure After Reperfusion

There was a nonsignificant trend in the reduction of heart failure after reperfusion in the trimetazidine group as compared with placebo (RR, 0.96; 95% CI, 0.86–1.08; $P = 0.50$). There was some heterogeneity based on the I^2 between the study populations for this analysis, but this was not statistically significant based on the P value ($\chi^2 = 3.75$, $df = 2$; $P = 0.15$; $I^2 = 47\%$).

Stent Restenosis

Trimetazidine was associated with significantly less stent restenosis as compared with placebo for acute coronary syndrome patients undergoing reperfusion (RR, 0.53; 95% CI, 0.34–0.83; $P = 0.006$).

Recurrence of Angina

There was a nonsignificant trend in the reduction of recurrent angina for trimetazidine as compared with placebo (RR, 0.95; 95% CI, 0.88–1.02; $P = 0.17$), with treatment duration ranging from 6 months to almost 4 years.

Reinfarction

The pooled analysis did not show a significant reduction in reinfarction among patients given trimetazidine versus placebo (RR, 0.89; 95% CI, 0.77–1.04; $P = 0.14$). No significant heterogeneity was reported among all four studies.

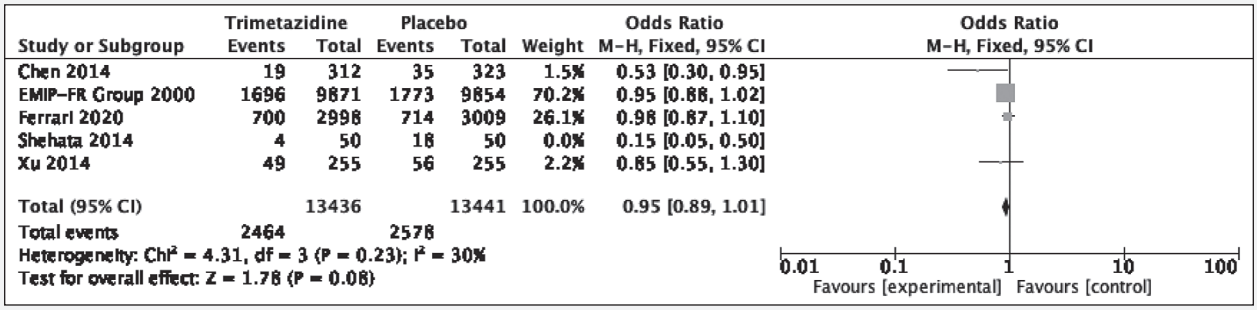

FIGURE 8. The effect of trimetazidine versus placebo on the incidence of major adverse cardiac events (fixed-effects model), with treatment duration of at least 1 year

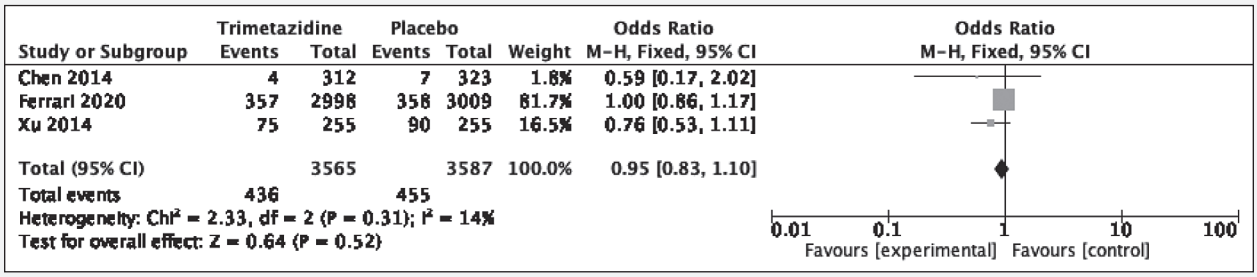

FIGURE 9. The effect of trimetazidine versus placebo on repeat target lesion revascularization (fixed-effects model)

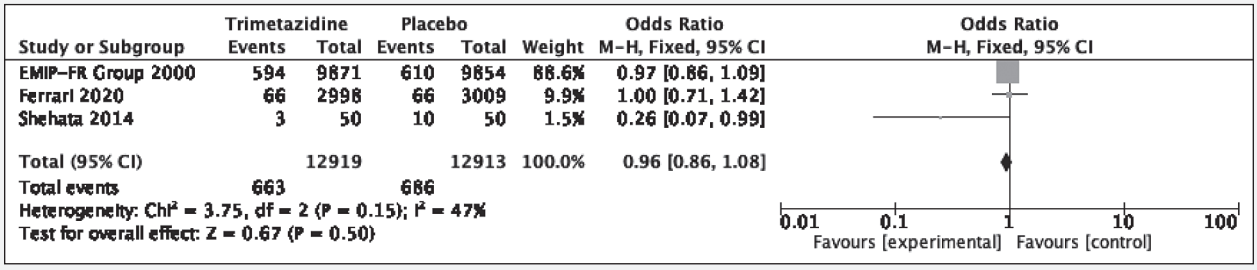

FIGURE 10. The effect of trimetazidine versus placebo on incidence of heart failure after reperfusion (fixed-effects model)

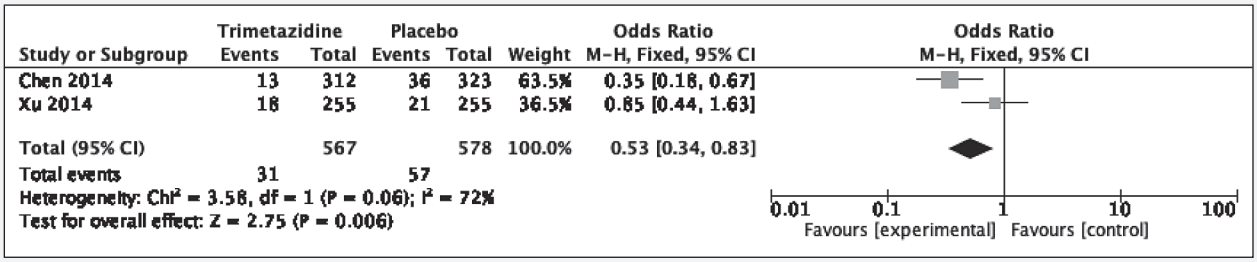

FIGURE 11. The effect of trimetazidine versus placebo on incidence of stent restenosis, (fixed-effects model)

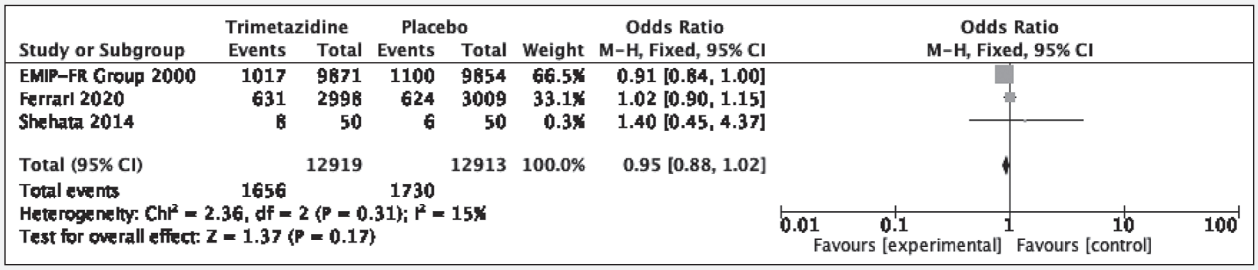

FIGURE 12. The effect of trimetazidine versus placebo on recurrence of angina (fixed-effects model)

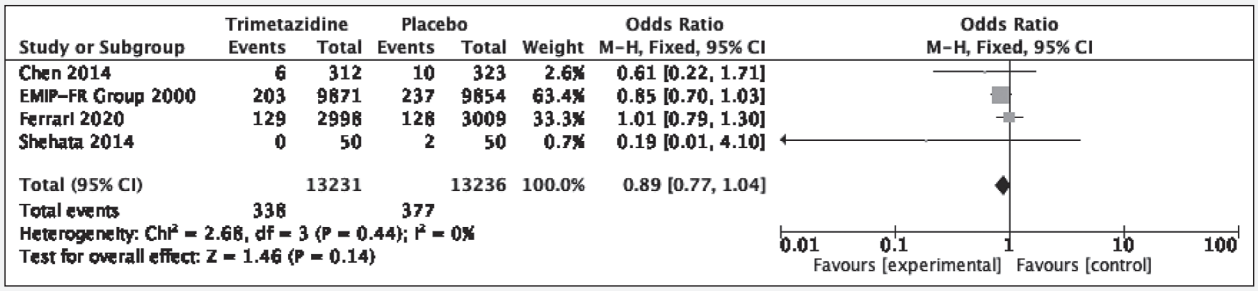

FIGURE 13. The effect of trimetazidine versus placebo on the incidence of reinfarction (fixed-effects model)

DISCUSSION

The current meta-analysis showed that trimetazidine was not associated with a significant reduction in cardiac mortality, revascularization, heart failure, recurrence of angina, and reinfarction as compared with placebo, for patients with acute coronary syndromes undergoing reperfusion. These results were similar to the recent meta-analysis by Li et al[3] on cardiovascular mortality but contrary to their findings on significantly lowered recurrence of angina and decreased hospitalization for heart failure. Their meta-analysis included only patients with acute myocardial infarction and with endpoints only until 6 months after discharge. The results of this pooled analysis may have been affected by certain factors such as the inclusion of trials with longer follow-up and patients who had chronic coronary syndrome (stable angina) who underwent elective PCI.

The ATPCI study, which was a large event-driven trial at 365 centers in 27 countries, included a well-treated and relatively young population, with mostly single-vessel coronary artery disease following successful PCI without complications. Any potential benefit of trimetazidine might have been attenuated because the study population was already routinely treated with β-blockers, calcium-channel blockers, or nitrates.[5] The patients in this study were not necessarily a higher risk group, such as that from higher risk ACS, HFrEF or those with severe left main and/or triple vessel disease. Therefore, the results may not be applicable to these groups. In the EMIP-FR Group study, trimetazidine was given for only up to 48 hours and not daily, unlike the other included trials. This could have contributed to the lack of significant benefit on clinical outcomes, with trimetazidine not being able to reach a steady state to achieve effect. Both studies had large study populations and gave much power to the pooled analysis.[8]

Peculiar to the current meta-analysis was the finding that trimetazidine was associated with a significant reduction in stent restenosis as compared with placebo. Trimetazidine has been shown to have an inhibitory effect on vascular smooth muscle cell proliferation and migration, which happen to be part of the neointimal proliferative pathophysiological process for (in-) stent restenosis.[9] Trimetazidine also improves endothelium-dependent relaxation, as determined by intra-arterial infusion of acetylcholine. It also decreases systemic oxidative marker

levels in patients with chronic heart failure from ischemic cardiomyopathy. Patients given trimetazidine had significant radial artery diameter improvement in response to acetylcholine infusion and had a greater peak oxygen uptake. There was also evidence of significantly reduced plasma oxidative markers. Such antioxidant properties may contribute to the improvement of endothelial dysfunction, hence preventing stent restenosis.[2] The researchers recommend further validation of these results when similar studies become available.

Further studies may be warranted to study the efficacy of trimetazidine in higher risk populations such as coronary artery disease patients who continue to have symptomatic angina despite reperfusion or in those with ischemic heart disease with left ventricular dysfunction, or in patients with acute coronary syndromes with severely stenosed vessels where reperfusion is not possible.

LIMITATIONS

Trimetazidine is relatively low cost and has been used commonly as part of the regimen either for acute coronary syndromes or for those patients with stable coronary artery disease, given previous meta-analyses showing benefit for the latter. Most of the studies reported a low risk of adverse effects, although this was not included in the analysis as the measure of outcomes varied between studies. Hence, the analysis is limited in evaluating for safe use of the drug. Trimetazidine may possibly be recommended for patients with coronary artery disease after reperfusion strategies to prevent stent restenosis. It would be worthwhile to reexamine the validity of these results in a larger randomized controlled trial. Future trials may include more focused study populations such as coronary artery disease patients who continue to have symptoms of ischemia despite reperfusion strategies. Larger RCTs with these higher risk populations may help us further understand the effect of TMZ in such patients and may likewise offset the heterogeneity observed in the results of the current study. This meta-analysis was also not able to include articles written in foreign languages, which could have widened the scope of valid randomized controlled trials.

CONCLUSION

In certain patients with coronary artery disease who have undergone reperfusion strategies, the addition of TMZ to optimal medical therapy does not significantly reduce cardiac mortality, repeat revascularization, heart failure, recurrence of angina, reinfarction, or total combined MACEs. However, there was an observed significant reduction of stent restenosis with trimetazidine as compared with placebo, which warrants careful consideration of the use of the drug in patients similar to the study's population.

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